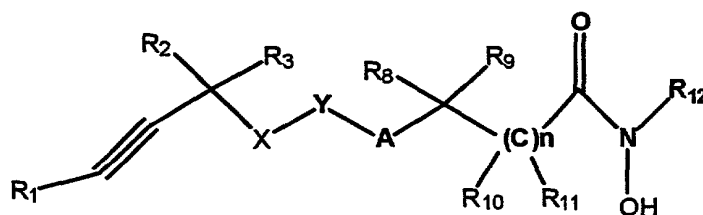


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CLAIMS

What is claimed:

- 5 1. A compound of formula



wherein:

- 10 R₁ is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C₅-C₈-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR₇, S and O;
- 15 R₂ and R₃ are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;
- R₅ is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C₄-C₈-cycloheteroalkyl;
- R₇ is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C₁-C₈ alkanoyl, COOR₅, COR₅, -SO₂-C₁-C₈ alkyl, -SO₂-aryl, -SO₂-heteroaryl, -CO-NHR₁;
- 20 R₈, R₉, R₁₀, and R₁₁ are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR₇, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR₇, O and S, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR₇, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;
- 25

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R₁₂ is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR₇, S and O, cycloalkyl of 3-6 carbon atoms, -C₅-C₈-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR₇, S and O, or alkyl of 1-6 carbon atoms;

5 A is O, S, SO, SO₂, NR₇, or CH₂;

X is O, S, SO, SO₂, NR₇, or CH₂;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

10

2. A compound of Claim 1 wherein Y is phenyl, pyridyl, thienyl, furanyl, imidazolyl, triazolyl or thiadiazolyl.

3. A compound of Claim 1 wherein R₂ and R₃ are each, independently, hydrogen or alkyl of 1-6 carbon atoms; R₁₂ is hydrogen; and Y is phenyl.

15

4. A compound of Claim 1 selected from the group consisting of:

2-(4-But-2-ynyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-3-pyridin-3-yl-propionamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-N-hydroxy-propionamide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionamide;

20

3-Biphenyl-4-yl-2-(4-but-2-ynyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-propionamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-octanoic acid hydroxamide;

2-(But-2-ynyloxy-benzenesulfonyl)-octanoic acid hydroxamide;

25

2[(R)-(4-Butyl-2-ynyloxy)-sulfinyl]-N-hydroxyoctanamide;

2[(S)-(4-Butyl-2-ynyloxy)-sulfinyl]-N-hydroxyoctanamide;

3-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-propionamide

4-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-butyramide;

- 2-(4-But-2-ynyloxy-phenoxy)-N-hydroxy-acetamide;
4-(4-But-2-ynyloxy-phenyl)-N-hydroxy-butyramide;
Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-5-
hydroxycarbamoyl-pentyl]-amide;
5 2-(4-But-2-ynyloxy-phenylsulfanyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-
yl)-acetyl-amino]-hexanoic acid hydroxyamide;
N-[5-(4-But-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-2-
phenethyl-benzamide;
2-(4-But-2-ynyloxy-phenylsulfanyl)-6-[2-(3,4-dichloro-phenyl)-acetyl-amino]-
10 hexanoic acid hydroxyamide;
Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-
5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-phenylsulfanyl)-6-(4-thiophen-2-yl-butyrylamino)-
hexanoic acid hydroxyamide;
15 9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-
5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-phenylsulfanyl)-6-diphenylacetyl-amino-
hexanoic acid hydroxyamide;
Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-phenylsulfanyl)-
20 5-hydroxycarbamoyl-pentyl]-amide;
6-(2-Benzo[b]thiophen-3-yl-acetyl-amino)-2-(4-but-2-ynyloxy-phenyl-
sulfanyl)-hexanoic acid hydroxyamide;
Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbamoyl-pentyl]-amide;
25 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-
yl)-acetyl-amino]-hexanoic acid hydroxyamide;
N-[5-(4-But-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-2-
phenethyl-benzamide;

- 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(3,4-dichloro-phenyl)-
acetyl-amino]-hexanoic acid hydroxyamide;
Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-5-
hydroxycarbamoyl-pentyl]-amide;
5 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(4-thiophen-2-yl-butyrylamino)-
hexanoic acid hydroxyamide;
9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfinyl)-6-diphenylacetyl-amino-hexanoic
10 acid hydroxyamide;
Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbamoyl-pentyl]-amide;
6-(2-Benzo[b]thiophen-3-yl-acetyl-amino)-2-(4-but-2-ynyloxy-benzene-
sulfinyl)-hexanoic acid hydroxyamide;
15 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(2-1H-indol-3-yl-acetyl-amino)-
hexanoic acid hydroxyamide;
Quinoline-2-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-
hydroxycarbamoyl-pentyl]-amide;
2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-
20 yl)-acetyl-amino]-hexanoic acid hydroxyamide;
N-[5-(4-But-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-2-
phenethyl-benzamide;
2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(3,4-dichloro-phenyl)-acetyl-
amino]-hexanoic acid hydroxyamide;
25 Quinoline-3-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-5-
5-hydroxycarbamoyl-pentyl]-amide;
9H-Xanthene-9-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-
5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-ynyloxy-benzenesulfonyl)-6-diphenylacetylaminohexanoic
acid hydroxyamide;

Isoquinoline-1-carboxylic acid [5-(4-but-2-ynyloxy-benzenesulfonyl)-
5-hydroxycarbamoyl-pentyl]-amide;

5 6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-ynyloxy-benzene-
sulfonyl)-hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-5-
hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

10 2-(4-But-2-ynyloxy-phenylsulfanyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-
isoindol-2-yl)-acetylamino]-acetylamino}hexanoic acid hydroxyamide;

N-{[5-(4-But-2-ynyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl-
carbamoyl]-methyl}-2-phenethyl-benzamide;

2-(4-But-2-ynyloxy-phenylsulfanyl)-6-{2-[2-(3,4-dichloro-phenyl)-
acetylamino]-acetylamino}-hexanoic acid hydroxyamide;

15 Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-
5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-
5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

20 2-(4-But-2-ynyloxy-phenylsulfanyl)-6-(2-diphenylacetylamino-acetylamino)-
hexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid {[5-(4-but-2-ynyloxy-phenylsulfanyl)-
5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-ynyloxy-phenyl-
sulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

25 6-[2-(2-Benzo[b]thiophen-3-yl-acetylamino)-acetylamino]-2-(4-but-2-
ynyloxy-phenylsulfanyl) hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

- 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-
isoindol-2-yl)-acetyl-amino]-acetyl-amino}-hexanoic acid hydroxyamide;
N-{[5-(4-But-2-ynyloxy-benzenesulfinyl)-5-hydroxycarbonyl-pentyl-
carbonyl]-methyl}-2-phenethyl-benzamide;
- 5 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-{2-[2-(3,4-dichloro-phenyl)-
acetyl-amino]-acetyl-amino}-hexanoic acid hydroxyamide;
Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbonyl-pentylcarbonyl]-methyl}amide;
- 10 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-[2-(4-thiophen-2-yl-
butyrylamino)-acetyl-amino]-hexanoic acid hydroxyamide;
9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfinyl)-
5-hydroxycarbonyl-pentylcarbonyl]-methyl}-amide;
- 2-(4-But-2-ynyloxy-benzenesulfinyl)-6-(2-diphenylacetyl-amino-acetyl-amino)-
hexanoic acid hydroxyamide;
- 15 1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-ynyloxy-benzene-
sulfinyl)-5-hydroxycarbonyl-pentylcarbonyl]-methyl}-amide ;
2-(4-But-2-ynyloxy-benzenesulfonyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-
isoindol-2-yl)-acetyl-amino]-acetyl-amino}-hexanoic acid hydroxyamide;
- 20 N-{[5-(4-But-2-ynyloxy-benzenesulfonyl)-5-hydroxycarbonyl-
pentylcarbonyl]-methyl}-2-phenethyl-benzamide;
2-(4-But-2-ynyloxy-benzenesulfonyl)-6-{2-[2-(3,4-dichloro-phenyl)-
acetyl-amino]-acetyl-amino}-hexanoic acid hydroxyamide;
- Quinoline-3-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-
5-hydroxycarbonyl-pentylcarbonyl]-methyl}amide;
- 25 9H-Xanthene-9-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-
5-hydroxycarbonyl-pentylcarbonyl]-methyl}-amide;
- 2-(4-But-2-ynyloxy-benzenesulfonyl)-6-(2-diphenylacetyl-amino-
acetyl-amino)-hexanoic acid hydroxyamide;

- Isoquinoline-1-carboxylic acid {[5-(4-but-2-ynyloxy-benzenesulfonyl)-
5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;
6-[2-(2-Benzo[b]thiophen-3-yl-acetylamino)-acetylamino]-2-(4-but-2-
ynyloxy benzenesulfonyl hexanoic acid hydroxyamide;
5 2-(4-But-2-ynyloxy-benzenesulfonyl)-6-[2-(2-1H-indol-3-yl-acetylamino)-
acetylamino]-hexanoic acid hydroxyamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-{4-[2-(1-
piperidinyloxy)ethoxy phenyl]butanamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-7-cyano-N-hydroxy heptanamide;
10 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-cyclohexyl-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-cyclohexyl-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-cyclohexyl-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(4-methoxyphenyl)
acetamide;
15 (2R)-2-{[4-(2-butynyloxy)phenyl] sulfinyl}-N-hydroxy-2-(4-methoxyphenyl)
ethanamide;
(2S)-2-{[4-(2-butynyloxy)phenyl] sulfinyl}-N-hydroxy-2-(4-methoxyphenyl)
ethanamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-methoxyphenyl)
20 acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(4-chlorophenyl)-N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl] sulfinyl}-2-(4-chlorophenyl) N-hydroxyacetamide;
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(4-chlorophenyl)-N-hydroxy-acetamide;
2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;
25 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;
2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxyacetamide;
(2S)-2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfinyl}-N-hydroxy-
acetamide;

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- (2R)-2-(4-bromophenyl)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl-N-hydroxy-
acetamide;
2-(4-bromophenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl-N-hydroxy-acetamide;
2{{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-[4-(2-thienyl)phenyl]-
5 acetamide;
(2R)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl}- N-hydroxy-2-[4-(2-thienyl)-
phenyl]ethanamide;
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[4-(2-thienyl)-
phenyl]acetamide;
10 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(1-naphthyl)acetamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfinyl}-N-hydroxy-2-(1-naphthyl)acetamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1-naphthyl)acetamide;
2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(4-fluorophenyl)-N-hydroxy-2-(1-
naphthyl)acetamide;
15 2-{{[4-(2-butynyloxy)phenyl]sulfinyl-2-(4-fluorophenyl)-N-hydroxyacetamide;
2-{{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-fluorophenyl)-N-hydroxyacetamide;
2-(2-methoxyphenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-
acetamide;
2-(2-methoxyphenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-N-hydroxy-
20 acetamide;
2-{{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(4-ethoxyphenyl) acetamide;
2-{{[4-(2-Butynyloxy)phenyl] sulfinyl-N-hydroxy-2-(4-ethoxyphenyl)
acetamide;
2-{{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-chlorophenyl)-N-hydroxyacetamide;
25 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(3-bromophenyl)
acetamide;
(2R)-2-{{[4-(2-butynyloxy)phenyl]sulfinyl-N-hydroxy-2-(3-bromophenyl)
acetamide;

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(2S)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl-N-hydroxy-2-(3-bromophenyl)
acetamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-(3-bromophenyl)-N-
hydroxyacetamide;

5 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-isopropyl-N-hydroxyacetamide;

R-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;

S-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;

2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-isoprpyl-N-hydroxyacetamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-phenyl-N-hydroxyacetamide;

10 R-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;

S-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(2-naphthyl)-N-hydroxyacetamide;

2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-(2-naphthyl)-N-hydroxyacetamide;

2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(2-naphthyl)-N-hydroxyacetamide;

15 Tert-butyl-4-[1-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(hydroxyamino)-2-
oxoethyl]-1-piperidine carboxylate;

2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-piperidinyl) acetamide;

2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[1-(4-methoxybenzyl)-4-
piperidinyl] acetamide;

20 2-(1-benzoyl-4-piperidinyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-
acetamide;

2-(1-acetyl-4-piperidinyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl-N-hydroxy-
acetamide;

25 2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-pyran-4yl-
acetamide;

2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-thiopyran-
4yl-acetamide;

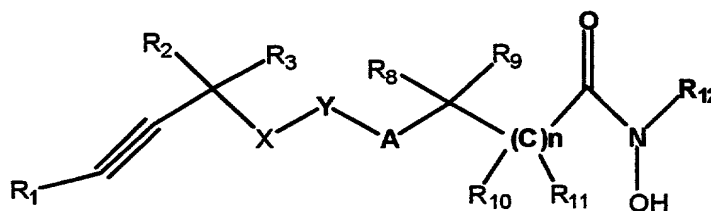
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2--[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1-oxidotetrahydro-2H-thiopyran-4-yl) acetamide; and
2--[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl) acetamide.

5

5. A method of inhibiting pathological changes mediated by TNF- α converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:

10



wherein:

- R_1 is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C5-C8-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR7, S and O;
- R_2 and R_3 are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;
- R_5 is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C4-C8-cycloheteroalkyl;
- R_7 is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C1-C8 alkanoyl, COOR5, COR5, -SO₂-C1-C8 alkyl, -SO₂-aryl, -SO₂-heteroaryl, -CO-NHR₁;
- R_8 , R_9 , R_{10} , and R_{11} are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, O

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and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR7, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

- 5 R₁₂ is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, S and O, cycloalkyl of 3-6 carbon atoms, -C5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO₂, NR₇, or CH₂;

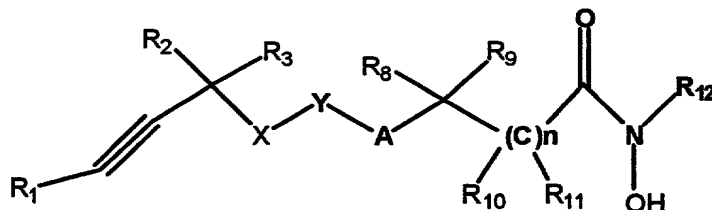
- 10 X is O, S, SO, SO₂, NR₇, or CH₂;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

- 15 6. The method of Claim 5 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

- 20 7. A pharmaceutical composition comprising a compound having the formula:



- 25 wherein:

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R₁ is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C₅-C₈-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR₇, S and O;

5 R₂ and R₃ are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

R₅ is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C₄-C₈-cycloheteralkyl;

10 R₇ is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C₁-C₈ alkanoyl, COOR₅, COR₅, -SO₂-C₁-C₈ alkyl, -SO₂-aryl, -SO₂-heteroaryl, -CO-NHR₁;

15 R₈, R₉, R₁₀, and R₁₁ are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR₇, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR₇, O and S, cycloalkyl of 3-6 carbon atoms, -C₄-C₈-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR₇, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

20 R₁₂ is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR₇, S and O, cycloalkyl of 3-6 carbon atoms, -C₅-C₈-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR₇, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO₂, NR₇, or CH₂;

X is O, S, SO, SO₂, NR₇, or CH₂;

25 Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.